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Panel Discussion on Cardiovascular Disease

Joseph Wu: This paper is now open for discussion. Would the discussants please proceed to the desk.

We'll have the first comment by Dr. Alan Armitage.

Alan Armitage: I would like to congratulate Dr. Wexler on his succinct presentation and to say that I agree with nearly everything that he has said. There's really not too much data and with six discussants all to say their bit, I will be selective in what I say and confine my comments to essentially pharmacological matters. The big question, of course, is whether exposure to ETS represents a health risk for the development of coronary artery disease. We need to remember that CHD is, of course, a common cause of death among nonsmokers. Moreover, although the public health body considers there to be a causal relationship between active cigarette smoking and development of CHD, Seltzer in particular has pointed out much that is not wholly consistent with such a story.

Dr. Wexler referred to five criteria that need to be considered in reviewing the ETS cardiovascular data. It is a good discipline to have this checklist approach and in addition, particularly when a situation is not clear cut, as is the case for ETS and cardiovascular disease, the sensitive, unbiased reviewer needs to have a common-sense "feel for the data."

There are three points I would like to add to the debate about biological plausibility.

First, the question of dosimetry is of particular interest to me because I am a pharmacologist. As we were told this morning, the effective dose of an ETS exposed individual is a function of the dynamic integration of concentration in various environments throughout the day and the time the nonsmoker spends in these environments. Assessing accurate dosage under real life conditions is therefore extremely difficult. Frankly, in many epidemiological studies, the assessment is no more than anecdotal. Merely knowing something about the spouse's or partner's smoking habits is not enough.

Since we are considering possible effects of ETS on the cardiovascular system, we must be concerned with systemic absorption rather than mere deposition. An individual exposed to the diluted smoke which is ETS cannot and does not absorb tobacco constituents such as nicotine and carbon monoxide to any significant degree, or any other putative cardiovascular toxicant like nitrogen dioxide. Thus, cotinine levels in biological fluids, which are generally considered to be a reasonable measurement of nicotine absorption of nonsmokers exposed to ETS, are approximately one percent of those measured in active smokers.

Now, in many studies the association between active smoking and CHD is much weaker, or even nonexistent, in female smokers than in male smokers. If in female active smokers an effect of smoking on the development of CHD cannot be convincingly demonstrated, I find it difficult to believe that such an effect is possible in female nonsmokers exposed to ETS (the favored subjects for epidemiological studies), unless there is something exceptionally noxious in ETS as compared to mainstream smoke.

A second point that to me casts doubt on the possibility of any significant role of ETS in the development of CHD concerns the pipe smoker. Pipe smokers inhale tobacco smoke actively to a limited extent. They also commonly surround themselves in a cloud of tobacco smoke so that they are probably exposed to the highest concentrations of ETS of any group. Yet, they enjoy relative immunity from the three major diseases associated with active smoking.

Finally, Dr. Wexler gave us some ideas on the definitive prospective study that he believes needs to be undertaken to answer the question I posed at the beginning of my commentary. Frankly, I would like to question the need for such a study. It will cost a lot of money that would probably be better spent on other, more important public health issues, as Dr. Roe has suggested. After all, cardiovascular diseases occupied only two pages of the 1986 Surgeon General's Report on the Health Consequences of Involuntary Smoking and did not feature at all in the Fourth Report of the U.K. Independent Committee on Smoking and Health.

So my clear advice to nonsmokers, of which I am one, and to those like me who are fond of good food, is to watch your weight, watch your diet, watch your blood pressure, but don't get too hung up about ETS.

Joseph Wu: Thank you. We will now hear comments from Dr. Joseph Fleiss.

Joseph Fleiss: In general, prospective cohort studies are prone to less serious bias and are subject to fewer sources of bias than are retrospective case-control studies. (Fleiss, J.L. (1981). *Statistical Methods for Rates and Proportions* (2nd ed.) Wiley, New York.) I believe that this general contrast between the two study designs holds for the published studies of the health effects of exposure to environmental tobacco smoke, so that the overall qual-

ity of the published studies seeking to associate exposure to ETS with coronary heart disease has been superior to the overall quality of the published studies seeking to link exposure to ETS with lung cancer. This is not to say that the former set of studies, all but one of which have been prospective, are free of bias. My comments, which do not duplicate those made by Dr. Wexler in his excellent review, shall be specific to the biases that may have affected some of the published cohort studies under consideration.

One kind of bias that should have no place in science is prejudgment: deciding beforehand what the final results should be, and then making statistical decisions and expressing the results so that the conclusions turn out the way they were supposed to. Consider, however, the 1985 study by Garland et al., one of the first to have been published. An inappropriate statistical decision the authors made was to perform one-tailed tests. That is, statistical significance would be declared only if the mortality rate of ischemic heart disease among nonsmoking women married to smokers was significantly greater than the mortality rate from ischemic heart disease among nonsmoking women married to nonsmokers. A difference in the other direction was ruled out a priori as either unimportant or unbelievable: "Since we were testing previous findings concerning the risk of passive smoking, statistical significance was assessed at one-sided p levels."

Their reasoning is flawed. The authors were not retesting previous findings. They were testing, for the first time as far as they knew, an association with ischemic heart disease. They were apparently unaware of the chapter by Hirayama that had appeared a year earlier (Hirayama, 1984). Even if theirs was the tenth study of the effect of ETS on ischemic heart disease, and even if each of the preceding nine showed a significant excess incidence in the group exposed to ETS, an attitude of open-mindedness would have led them to a two-tailed test.

I was sorry to see sanction given to one-tailed tests in the 1986 Surgeon General's report on ETS: "Given the strength of the evidence on active smoking and disease risk, one-sided testing in the direction of an adverse effect seems appropriate for most potential consequences of ETS." I have argued publicly that one-tailed tests are almost never appropriate in randomized clinical trials (Fleiss, J.L. (1987). Some thoughts on two-tailed tests. *Control Clin. Trials* 8: 394: Fleiss, J.L. (1989) One-tailed versus two tailed tests: Rebuttal. *Control Clin. Trials* 10: 227–230.), and do not see any valid reasons to excuse epidemiological studies from the requirement for two-tailed tests. More is at stake than the impossibility, with a one-tailed test, of ever finding that nonsmokers exposed to ETS might be at significantly less risk than those not exposed. Biased decisions might be made concerning which potential confounding variables to control for and which not if a difference in the "wrong" direction has been ruled out: a potential confounder that moves the odds ratio or hazard ratio in the hypothesized direction may be more likely

to be included in the analysis than one that moves the measure of association in the "impossible" or "unimportant" direction. I am not suggesting that this kind of error actually occurred, only that preconceptions as to the possible direction of association invite biased judgments.

After adjusting for differences between the exposed and unexposed cohorts in risk factors for heart disease, Garland et al. found the relative risk for death from ischemic heart disease to be 2.7, with a one-tailed p-value less than 0.10. (Recall that this corresponds to a traditional two-tailed p-value of $p<0.20$.) The authors concluded that "these data are compatible with the hypothesis that passive cigarette smoking carries an excess risk of fatal ischemic heart disease." Not stated is the fact that the range of uncertainty is so great (the 95% confidence intervals for the relative risk extends from approximately 0.6 to over 12.0) that the data are also compatible with no excess risk and with a markedly reduced risk of fatal ischemic heart disease among those exposed to ETS. Data that are compatible with so many contradictory hypotheses are really compatible with no hypothesis.

The statistical criteria used by Svendsen et al. in their 1987 paper were more appropriate than those used by Garland et al. But the statement of their major conclusion reveals a similar possibility of prejudgment: "Our findings . . . support the hypothesis that passive smoking is associated with an increase in morbidity and mortality among nonsmokers." The only morbidity studied by the authors was coronary heart disease morbidity, and it was analyzed only in conjunction with coronary heart disease mortality. None of the relative risks for the composite endpoint of fatal or nonfatal coronary heart disease was significant at the 0.05 level, even without control for multiple comparison artifacts. Once again, the findings support a number of difference hypotheses, not just the one stated by the authors.

I mentioned a 1984 chapter by Hirayama in which, apparently for the first time, a statistically significant association was reported between a nonsmoking women's exposure to ETS and her risk of dying from ischemic heart disease. There are several problems with Hirayama's analyses. One concerns his erroneously presenting values of critical ratios as values of chi-square. The problem is not a trivial one because the same error was pointed out to him some years earlier in letters written in response to his initial paper linking exposure of ETS with lung cancer (Hirayama, 1981). Another example of possible sloppiness is found in one of his tables (Table 7). When numbers of deaths are first subdivided by the spouse's age group, and are then subdivided by the spouse's age group as well as the spouse's occupation, one expects some reduction in the numbers because of missing data. The last thing one expects are increases in the numbers; that is, more deaths with information on two characteristics than with information on one. Nevertheless, this is exactly what happened.

One must wonder what other statistical mistakes Hirayama has persisted

in making. Consider his persistence in controlling for the age of the husband when analyzing data for the wife. This curious and basically indefensible feature of his analytic strategy was also pointed out to him in the correspondence that followed his first paper (Hirayama, 1981) but he never responded adequately. The reason wasn't the unavailability of the wife's age because he finally presented results for lung cancer that controlled for the wife's age in the same chapter in which he presented his results for ischemic heart disease (see his Table 2 on p. 180).

A striking feature of Hirayama's data for ischemic heart disease mortality in nonsmoking wives is that an association with the husband's smoking emerges only after the husband's age is adjusted for:

Smoking Habit of Husband	*Odds Ratio**	
	Before Adjustment	*After Adjustment*
Ex-smoker or 1–19 per day	1.01	1.10 (n.s.)
More than 20 per day	0.99	1.31 ($p<0.05$)

*Versus nonsmoking husbands as the control group.

Until Hirayama analyzes his heart disease data sensibly by adjusting for the effect of the wife's age and not her husband's, and adjusting for the effects of other confounders, I suggest that his findings not be taken seriously.

Peter Lee: Dr. Wexler gave a careful presentation on ETS and cardiovascular disease and I agree completely with his conclusion that the existing epidemiological evidence is inadequate to provide proof of a cause and effect relationship.

I would like to draw attention to a number of points that may assist discussion of this important issue. First, I would like to point out that there is, in fact, a small amount of information in addition to that cited by Dr. Wexler. In his 1988 meta-analysis paper, Wells reports the results of a non-published 1986 study by Martin et al. in Utah purporting to find a statistically significant relative risk of 2.6 despite being based on a total of only twenty-three deaths or cases of CHD. (Wells, A.J. (1988). An estimate of adult mortality in the United States from passive smoking. *Environment Int.* 14: 249–265.)

So we've actually got seven epidemiological studies, six of which report a positive association. Of the six, four of them, Hirayama, Helsing, Martin and Hole report a statistically significant result, either in trend analysis or in simple comparison of ETS-exposed and non-exposed subjects. Garland, Hole, Martin and Svendsen report a relative risk in excess of two (more than a 100% increase in risk) in relation to ETS exposure. In comparison, a mass

of literature from large prospective studies shows that active smoking, on average, is associated only with a 60% to 80% increase in risk of heart disease. Given that ETS-exposed nonsmokers are far less exposed to smoke constituents than are active smokers, and also that active smokers have more ETS exposure than ETS-exposed nonsmokers, these results just seem to me to lack plausibility, a priori. They seem far more likely to result from chance or bias than to represent a real effect.

One form of bias that may be particularly important in assessing the relationship between ETS and heart disease is the possibility of publication bias. When you look at the overall literature you see that the total number of reported deaths or cases in ETS studies involving heart disease is similar to those involving lung cancer. When one considers that the incidence of heart disease death in nonsmokers is vastly more common than lung cancer deaths in nonsmokers by a factor of about fifty, it's really rather surprising that so few even moderately sized studies of heart disease and ETS have been published.

Dr. Wexler suggests that the Framingham study might be able to provide data, but really this is only a relatively small study of a few thousand people. Surely the most obvious place to look for more information is the American Cancer Society's Million Person Study. They have published results on ETS and lung cancer involving a hundred and fifty-three deaths. (Garfinkel L. (1981). Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. *J. Natl. Cancer Inst.* 66: 1061–1066.) They certainly have the information to publish results on ETS and heart disease involving, I would imagine, five to ten thousand deaths. The obvious question arises, does failure to publish mean no association was found? Because if that in fact were the case, this would cause an absolutely enormous distortion of the overall evidence.

If you look at the seven published studies on ETS and heart disease, only Helsing's and Hirayama's are based on any sort of substantial numbers of deaths at all. I just want to add a few points regarding these two studies.

First, I note some further weaknesses in the Helsing study. There was no adjustment for number of people in the household. Helsing was comparing people who lived with a smoker and those who did not. So, for instance, people who lived on their own automatically went into the category of people who didn't live with a smoker. There's obvious scope for confounding with factors relating to living alone, overcrowding, etc. The study was also not actually about the probability of dying but about the probability of dying within Washington County, as I understand it. They made no attempt to get death certificates for people who moved outside this relatively small area of the United States. If smoking, ETS exposure or household size related to the probability of leaving the county, bias would result. In contrast, I noticed in the British doctors' study that they took enormous pains to follow up the thirty thousand or so doctors involved. They chased people to the ends of the

globe to find out what they died of and I think they only failed to track down fifty or sixty, mainly those doctors who had gone back to India and had gotten lost in the subcontinent somewhere.

The Helsing study also used statistical adjustments by a procedure that wasn't really clear and which had an enormous effect on the relative risk estimates. In women he had an unadjusted 34% reduction in risk which he put through his magical unexplained statistical machine and got a 24% increase. So I'd really like to see rather more before accepting anything from this study.

The only other study with substantially more than 100 deaths is that of Hirayama. Dr. Wexler's paper dealt at length with the weaknesses of this study and he quoted the results on the first two lines in his text. The fact that there was a nonsignificant relationship in 1981 and a significant relationship in 1984 is intriguing. The first result was based on 404 deaths, the next on a further 88, and the analysis was essentially the same apart from the fact that in the first analysis he standardized for age and occupation, in the second analysis, only for age.

Now, if you assume occupational standardization made no difference, you can actually calculate what the relative risks were for the intervening period. You've got this enormously strong relative risk of five. You can also show that there's very highly significant heterogeneity of relative risk between the first period up to 1981 and the period thereafter. But if, in fact, you can't do this because standardization of occupation did have an effect, well why on earth didn't Hirayama standardize for it in 1984? So it seems not to make sense either way.

The question finally is whether a new study is actually worth doing. Dr. Wexler noted that existing data are inadequate for proof of cause and effect and proposed that a large study be carried out. The problem, it seems to me, is that given what we know about the association of active smoking with heart disease and the relative exposure to ETS of nonsmokers, it seems highly implausible that even in the most ETS-exposed nonsmokers you get a relative risk of more than two. I believe Dr. Wexler said in his paper that he feels one actually requires a relative risk of two or more as a precondition to prove causality.

So if that's the case, what's the point of doing the study? Although I believe that a good study can pick up relative risks of less than two, I have my doubts that any study could pick up an effect of the order of magnitude which could plausibly exist in this case.

Joseph Wu: Comments by Dr. Lorimer?

Ross Lorimer: The studies that Dr. Wexler very ably and very extensively reviewed are a testimony to the diligence of medical investigators. More than 100,000 individuals have been assessed from the point of view of cardiovascular disease and ETS and we still have no definite answers, although we do have some impressions.

The question of a meta-analysis of results has been considered. Certainly the Surgeon General's report of 1986 suggested this possibility. Further data have accumulated since then. From the cardiological point of view, there is no doubt that in certain situations meta-analysis has been useful. For example, the use of beta blockade following myocardial infarction has been well substantiated by the use of meta-analysis. The effect of lowering cholesterol levels on the subsequent incidence of coronary heart disease has been shown to be a worthwhile clinical exercise by this method. These studies have employed finite end points, such as survival, and variables, such as cholesterol levels, which can be standardized. Under these circumstances, it is relatively easy for different populations to be compared. However, meta-analysis of the relationship between cardiovascular disease and ETS involves comparing such disparate groups as an agricultural population of Japanese women with a group of Californian women living in a retirement community. The MRFIT/ETS study evaluates American men who are already at increased risk from coronary disease because of raised cholesterol and high blood pressure. This would be compared with a group of men and women with a different range of risk factors living in the environment of the west of Scotland. In these situations, it may be that meta-analysis is not appropriate.

There has been considerable discussion today regarding the Hole study from the west of Scotland. I would like to review their data regarding coronary heart disease deaths. In the control group, there were index case nonsmokers living with nonsmokers. In the ETS exposed group-index case nonsmokers were living with cigarette smokers. The single exposure group were index case smokers living with nonsmokers and in the double exposure group both co-habitants smoked. There were 30 deaths from coronary heart disease in the control group where neither partner smoked. On a pro rata numerical basis one might have anticipated around 48 to 49 deaths in the ETS exposed group. Fifty-four deaths did occur, an excess of only five or six. It is important, however, to recognize that correction of data for age, sex, blood pressure, cholesterol and social class did show a significant increase ($p < 0.008$) for relative risk of coronary heart disease. In the MRFIT study, on a pro rata basis there would appear to be two excess deaths from coronary heart disease and four extra myocardial infarctions. Again, this was a study involving a large number of people followed for around seven and a half years and statistical analysis did suggest an association between ETS and coronary heart disease, although this did not achieve formal statistical significance.

While we can discuss the merits or demerits of the various statistical approaches, it would appear that the actual number of extra deaths is relatively small. From the clinical point of view, I would agree with Dr. Armitage that the important factors with regard to coronary disease are active cigarette smoking, high blood pressure, high cholesterol, life style, and employment or unemployment. There may well be other factors involved. However, it seems

unlikely that ETS is contributing significantly to the incidence of coronary heart disease. I would also think it unlikely that it would be possible to confirm or refute this suggestion by mounting a further long-term study. The studies report a small adverse association of ETS and coronary heart disease at most. Any further study would require an extremely large population followed for a very long period of time. This simply may not be possible as a practical matter.

Joseph Wu: We now have comments from Dr. Max Weetman.

Max Weetman: I've had this all my life, beginning with "W" and having most functions in life allocated according to the starting letter of your name. Everything's been said. I've really got very little to add. I'd like to congratulate Dr. Wexler on a really very thorough job of going through the various cases.

I think most of the points have been made here, but I've not come as far as this to actually say nothing, so I want to consider a new "ology". We've talked epidemiology, dosology, and things of this nature. But there's really a rather more fundamental "ology" that we ought to consider, and that's epistemology.

Epistemology is what can we know, what is knowable.

We can't know very much about ETS and cardivascular diseases, I think, because of the problems I will outline here. I would consider all of these problems to be design problems. I'm not going to go through all of them in fine detail, but I have a few points I want to make. Everything I say here applies equally to cancer of the lung as well.

The first weakness really stems from our measurement of exposure to ETS. The best way to control this would be to experiment in a reaction chamber, where you can actually monitor certain surrogates for environmental tobacco smoke and control the number of cigarettes smoked.

Once you go beyond this, to a real world situation, or into a retrospective look at somebody's lifestyle, epidemiology begins to lose all credibility. It's really guessology with respect to exposure at this stage.

Now, how do we actually find out about what possible exposure one might have suffered? We do it by asking people. We ask, "Did you smoke? Did your husband smoke? Did your wife smoke?," etc. Obviously, this approach is prone to an enormous degree of error. We're not likely to get a particularly accurate and true answer there.

Another problem, particularly true for studies of cardiovascular disease, is the use of selected populations. Taking the Multiple Risk Factor Intervention Trial, for example, the patients had high serum cholesterol levels and high blood pressure. In addition, they drank rather more than the control group. Why do we rely on this high risk group for information? Perhaps it's going to tell us something that "normal people"—whatever that might mean—wouldn't.

The second trial where we get some positive information is the noto-

rious—I would say—Hirayama trial. There are even more things wrong with it than have been said here. It's tremendously unrepresentative of the population of Japan because it includes far too few old people, over eighty.

Now, why do we use these peculiar things, the Japanese or high risk or atypical groups, like Hirayama's Japanese cohort or those in the MRFIT? It's because ETS as a problem is quite a recent event. It started with Trichopolous and Hirayama himself in about 1981. Most of the trials considered today did not originate as studies of exposure to ETS, but as studies of other phenomenon, that have been adapted to consider ETS.

The Multiple Risk Factor Intervention Trial had been running for some time. Hirayama's trial was already about twelve or thirteen years old before he started to seek information about ETS exposure.

Epistemologically speaking, the result of this is that you are preselecting the study group, so you have too few subjects to resolve the question. The Garland trial had two deaths in the control group. It's far too brittle a number for a baseline. You can't draw any conclusions about common disease from such small groups.

The use of death certificates is another problem. Not all the trials use death certificates. There are some exemplary attempts where physicians actually review the case to determine the likely cause of death and guard against error. But a lot of the trials, including Hirayama's, use a death certificate only. These are, we know, notoriously inaccurate.

Now, the only thing I would really argue about with our eminent opening speaker involves a little bit of philosophy; I'm talking about biological plausibility. Asking questions about biological plausibility can sometimes be misleading. The worst case arises when you've got a rather weak P-value: you're not quite there but you obviously would like to get there. You then list a number of factors that, had you continued, would have caused you to reach the desired result. You then ask, is it a biologically plausible event that this result will occur? To me, if biological plausibility is used in this sense, it really means "in the absence of evidence, I will now cast one further card, a weak one though it be." The purpose is to fit the results to the preconception brought by the scientist to the experiment. As has already been said, this is the antithesis of scientific investigation. It's wish fulfillment. Maybe our grant bodies are partly responsible for this. We have to publish more and more papers, even though some of them may be nonsense, so that we can obtain the next grant, and do the next run of work.

Similarly, with respect to biological plausibility, Peter Lee has very clearly pointed out that if you have eight factories in quite different places, and people die from some rare disease all having been involved in the same industrial process, you don't say, "Well, I can't see how it's working biologically." If you think about what we know biologically, most things are absurd in the first

place, and the rationality in which we place them comes after the initiating discovery.

This is certainly true for most new types of drugs that are discovered. It's interesting to note that carbonic anhydrase had been demonstrated in the stomach many years ago, and was only then discovered in the kidney when they first used sulfonamides and obtained a diuretic response. The only way you could explain this diuretic response was by actually postulating that this enzyme was there and sulfonamides inhibited it. So quite often you get something amazing, biologically implausible and that then promotes discoveries that result in a rational background being discovered.

I think a more economical phrase that we ought to try and use, if we have to be stuck with this notion of biological plausibility, is "freedom from biological implausibility." That's putting the boot on the other foot and asking people to do a little bit of thinking rather than just justifying their orignal thoughts.

Joseph Wu: We'll have the comments from Dr. Philip Witorsch.

Philip Witorsch: Like Max Weetman, I've spent most of my life being at the end of the list. I therefore decided to comment briefly on an aspect that none of the other speakers has addressed, namely the acute effects of ETS exposure on individuals with pre-existing coronary artery disease. Dr. Wexler very eloquently critiqued the Aronow study but there is another, very good study that was published in 1987 by Sheps et al. from the University of North Carolina. The Sheps study raises the issue of the biological implausibility of the acute effects postulated by Aronow.

Aronow and others have suggested that the acute effects of ETS exposure with regard to exacerbation of angina in individuals with pre-existing coronary artery disease relate, at least partially, to elevation of carboxyhaemoglobin from ETS exposure. Superficially, this sounds like it might make sense, until you think about the amount of carbon monoxide actually generated from ETS. Studies have shown only a slight difference in the levels of carboxyhaemoglobin in nonsmokers exposed to ETS as compared to those in nonsmokers not exposed. This result causes the hypothesis to lose its plausibility.

The Sheps study examined thirty individuals with well- documented coronary artery disease and symptomatic angina who had documentation of electrocardiographic changes on exercise typical of angina. They exposed these individuals in an exposure chamber to carbon monoxide, using an endpoint of approximately four percent carboxyhaemoglobin. That compares to levels usually found in nonsmokers and in their controls of about 1.5% carboxyhaemoglobin.

Interestingly, to achieve the 4% carboxyhaemoglobin they had to expose their subjects to one hundred parts per million of carbon monoxide in air for a period of an hour or more. This is probably three to five times the level of

carbon monoxide that has been measured in very smoke-polluted areas. They exercised these individuals and measured a variety of cardiovascular parameters, including electrocardiographic evidence of angina, ST-T wave changes, radionuclide imaging of the heart, ejection fraction, and a number of other cardiovascular indices.

They found absolutely no effect on the duration to onset of angina, or any of the objective cardiovascular parameters, despite the subjects' exposure to a hundred parts per million of carbon monoxide and a carboxyhaemoglobin level approaching four percent.

The Sheps study, when added to all the deficiencies cited relative to the Aronow study, should lay this issue to rest. It's very clear that in a real-life situation it is biologically implausible for the degree of carbon monoxide exposure related to ETS to have any effect as far as exacerbation of angina.

I think this might have implications for studies of ETS and reproductive effects as well. Frank Sullivan mentioned earlier that carboxyhaemoglobin is thought possibly to play a role relative to reproductive effects. But it appears implausible that the degree of real-life exposure to ETS results in any significant changes in carboxyhaemoglobin.

Joseph Wu: We have time for a couple of additional comments or questions from the floor. Dr. Roe.

Francis Roe: If I could just address a question to the panel in general. I have the impression that coronary heart disease is not a single disease but at least two. Coronary heart disease in men under the age of fifty seems to be related to different factors than CHD occurring from age sixty onwards. These seem to be two different diseases, but maybe there are many others. I wonder what the implications of this are in relation to studies of ETS.

Secondly, from a causative point of view, one would be concerned with two things. The first is the set of factors that cause arteriosclerosis, and the second is the set of factors that make a fatal coronary occlusion more likely in a person with arteriosclerosis. They seem to be two different things. Aronow obviously was looking at the second of these. The first should not be overlooked.

In examining carcinogenesis, I earlier stressed the point that you need to know what an individual has been exposed to from childhood in order to get any reliable feeling of what happens in lung cancer risk. I suggested that this has not been done so far.

Now, isn't this also true of cardiovascular disease? I mean, the idea of Aronow collecting a lot of old gentlemen and sticking them all on exercise bicycles, to me, is horrific. Would we not be better off if we really started such studies with younger people?

Peter Lee: I would comment on the second of Dr. Roe's points. I suspect lifetime exposure isn't so important in heart disease as it is in respiratory disease. If one takes the analog of active smoking, the evidence seems to

suggest that current smoking is important and ex-smoking is not really important because if you give up smoking, your risk reverts fairly quickly. Yet, there may still be something in it even so.

Ross Lorimer: A similar problem arises in studies of women. Coronary artery disease in women expresses itself differently than in men insofar as pre-menopausal women are concerned. From a clinical point of view, the coronary heart disease occurring in women also is usually associated with much smaller diameter of coronary vessels with more diffuse disease than in young men with myocardial infarction, in whom it is not unusual to find single vessel disease, especially involving the left anterior descending and having an acute thrombotic episode. So I'm sure you're absolutely right.

Philip Witorsch: If I can just add a brief comment. I agree that there are different diseases involved. I think lifetime factors are important, but not necessarily lifetime ETS exposure or lifetime cigarette smoking. In many of these studies, people tend to forget that perhaps the most important determinant of coronary artery disease is the choice of parents that one makes. Added to that are diet, lifestyle, exercise and a whole host of other factors, all of which have been very poorly controlled for in the studies to date and are, frankly, very difficult to control for. Assessing cholesterol levels is not an adequate control of many of these factors and that's, perhaps, the most that's been done. It's very analogous to the token control for socio-economic status that has been done in a lot of studies.

Jarnail Singh: I have been doing research on the effect of carbon monoxide levels in animals since 1972. I have a series of papers and a series of experiments where I expose mice from when they are newly born, three, four days old, until they are about eight weeks old. The mice are constantly exposed, except during cleaning and watering, to three levels of CO, 25 PPM, 50 PPM and 100 PPM. At the end of eight weeks, we sacrifice the animals, take all the tissues, lungs, hearts, spleen and kidney, and send them to a pathologist to determine whether there is any dose-dependent effect on these organs. The conclusion is that at these levels, 25, 50 and 100 PPM, there is no dose-dependent effect on the heart or on the lungs.